CAUSAL THERAPEUTICS

IN THE

INFECTIOUS DISEASES.

J. C. WILSON, M.D.

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Read before the Association of American Physicians at its third annual meeting, held at Washington, D.C., September 18 to 20, 1888.

A CLINICAL EXPERIMENT

(ENTERIC FEVER—PHTHISIS).

BY J. C. WILSON, M.D.,

PHILADELPHIA, PA.,

Attending Physician to the Philadelphia Hospital and to the Jefferson Hospital.

THE discoveries of Hoffa, Brieger, Vaughan, Bourget, and others within the last few years have done much to clear up the relation between the special pathogenic germs of the infectious diseases and their symptomatology. They have also rendered necessary a new definition of the infectious diseases. In the words of Vaughan and Hovy,* "An infectious disease arises when a specific, pathogenic microorganism, having gained admittance to the body, and having found the conditions favorable, grows and multiplies, and in so doing elaborates a chemical poison which induces its characteristic effects."

The germ theory as a working hypothesis has revolutionized surgery and robbed midwifery of the chief of its terrors. It has given us an antiseptic procedure which reaches the perfection of simplicity in ideal cleanliness and recently-boiled water. It has made quarantine reasonable, preventive medicine a power, and prophylactic measures intelligible to the people. Isolation and disinfection have now an obvious and definite

* "Ptomaïnes and Leucomaïnes," 1888.

purpose. But until it came to be known that pathogenic micro-organisms produced the definite chemical poisons called ptomaïnes the demonstrated facts of bacteriology shed but little light upon the clinical phenomena of the infectious diseases; still less did they directly influence treatment except locally. For countless investigations have shown that antiseptic medication by way of the mouth has little effect upon the specific bacteria of a developed disease. Nevertheless, despite innumerable failures, something has already been accomplished, and, to quote Welch,* "One need not be of a very sanguine temperament to hope that our steadily-increasing knowledge will bear fruit, not only, as in the past, in the prevention of these diseases, but also in a rational system of causal therapeutics."

The production of special ptomaïnes by specific bacteria is probably a necessity of the growth and multiplication of these bacteria, and that which interferes with the splitting up of the complex chemical compounds of the body proportionately interferes with that growth and multiplication. It is in this way, doubtless, that antiseptics render organic substances insusceptible to the action of putrefactive germs rather than by direct action upon the germs themselves.

What may be the mode of action of vaccination or of the inoculation of attenuated virus is at present past finding out, but the effects are manifested upon the tissues and the fluids of the body. It is by acting upon the substances that constitute the culture media of the bacteria that their growth and multiplication are to be interfered with by therapeutic means, rather than by directly acting upon the bacteria themselves when they have already invaded the organism and caused disease.

The cases which form the basis of this communication are submitted to your consideration as illustrations of a mode of treatment not hitherto employed in enteric fever and pulmonary tuberculosis. I have no theory to offer to the Association as to whether or not the salts of mercury undergo possible

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* "Modes of Infection." Annual Address, 1887.

modifications when taken by the mouth, which they escape when administered hypodermically, nor as to possible differences in their effects when undergoing slow absorption and acting continuously, as compared with their action when given in separate doses in a form permitting rapid absorption and elimination.

The cases are submitted as a contribution to the subject of causal or etiological therapeutics in contradistinction to all forms of symptomatic and expectant treatment.

Rendot,* in 1887, treated with satisfactory results a series of cases of enteric fever by the administration of mercuric chloride in daily doses of from 2 to 5 milligrammes ($\frac{1}{32}$ to $\frac{1}{12}$ grain). This quantity was given in divided doses at intervals of two hours. To the objection that in these minute doses the drug is inadequate to produce physiological effects, Dr. Rendot replies that the doses are scientifically rational, and that they fulfil a positive indication of the typhoid infection. They are insufficient to destroy the vitality of the bacteria of typhoid fever, but possess, he believes, the power of neutralizing the toxic principles produced by their functional activity. Is it not possible that the action of the mercuric chloride tends rather to restrain the formation of these toxic principles?

Some months ago, while investigating the method of treating syphilis by the intramuscular injection of calomel, as first suggested in 1864 by Scarenzio and revived in 1885 by Neisser, it occurred to me that this plan might prove valuable in other forms of infection.† It has certain definite advantages over the ordinary methods of medication, among which are infrequent administration, precision of dosage, and promptness of action. As the calomel thus introduced into the organism undergoes gradual conversion into the albuminate of mercury, and, in the presence of the alkaline fluids of the tissues, into a double chloride of mercury and sodium,

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* *Gaz. Hebdom. Sciences Méd.*, Bordeaux, December 11, 1887.

† J. C. Wilson, M.D., "Note on the Treatment of Syphilis by the Hypodermic Injection of Calomel" (*Medical News*, June 2, 1888).

this method has the further advantage of exposing the organism to the continuous action of mercury in small amounts. It, moreover, possesses the cardinal advantages of sparing the digestive tract all direct irritation, and the certainty of absorption without regard to the state of the alimentary canal.

The calomel is suspended in a mixture of glycerin and water, and injected deeply into the gluteal or deltoid muscles under rigid antiseptic precautions. The operation is usually followed by transient pain, and by circumscribed irritation and deep induration; if properly performed, abscesses do not follow. The induration usually disappears in the course of a week. The dose of calomel injected is 1 to 2 grains; it is repeated every four or five days. I have no experience with the red oxide of mercury used in this way, nor with the "gray oil" of Lang.

ENTERIC FEVER.

CASE I.—E. G., male, æt. 31, unmarried, Italian seaman, was admitted to the medical ward of the Jefferson Medical College Hospital on the 1st of November, 1887, on the eighth day of an attack of enteric fever, contracted while aboard ship in the Delaware River, opposite Philadelphia. The evening temperature on three occasions after his admission to the ward reached 105° F.; the morning temperature range was about 103° F. The temperature fell to normal on the twenty-first day of the attack, and, with the exception of occasional transient febrile exacerbations, remained at the normal until the fortieth day. During this time, however, it was noted that the area of splenic dulness continued to be enlarged. On the fortieth day a relapse occurred, with recurrence of the rash and diarrhœa, and the febrile movement reached 103° F. This relapse was complicated by the occurrence of a large abscess in the left inguinal region. Defervescence was complete on the fifty-ninth day from the beginning of the primary attack and the nineteenth day from the beginning of the relapse. From this time convalescence was uninterrupted. Hypodermic injections of calomel in grain doses were employed in this case throughout,

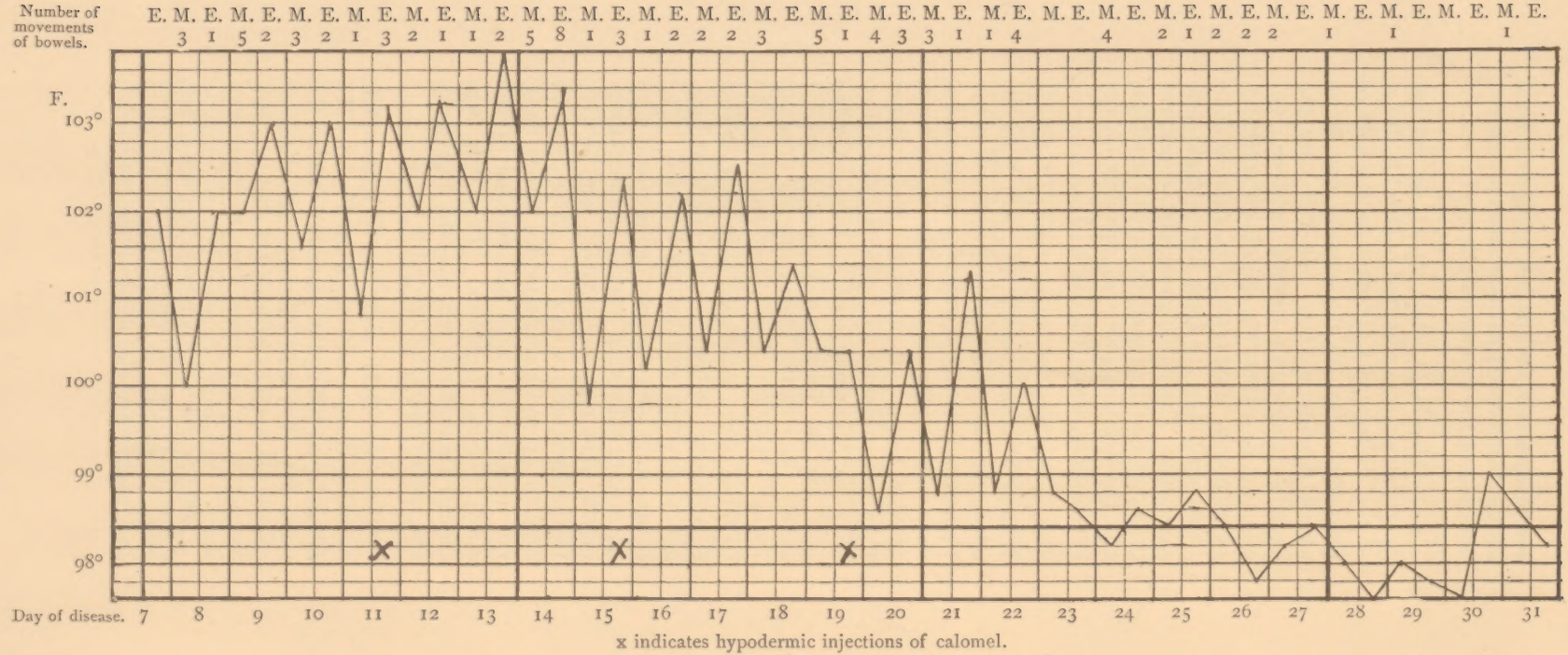
the administration of the dose being on several occasions followed by a distinct and permanent lowering of the temperature range.*

CASE II.—H. O., male, æt. 21, an acrobat by profession, was admitted to Ward 8, Bed 5, of the Philadelphia Hospital, on the 19th of December, 1887, on the seventh day of an attack of enteric fever. In this case the evening temperature ranged between 103° and 104° F. There was splenic enlargement, no tympany, scanty eruption, copious diarrhœa, amounting to from five to eight passages daily. The morning temperature reached the normal on the twentieth day of the attack, and the defervescence was complete on the twenty-third day. (See Chart I.)

CASE III.—J. C., male, æt. 24, born in Ireland, a laborer, unmarried, had been for a long time an inmate of Ward 8, Bed 6, of the Philadelphia Hospital, suffering from pulmonary consumption affecting the upper lobes of both lungs, with cavities. While absent from the hospital on leave in November, 1887, he contracted enteric fever. On the fifth day the evening temperature reached 104° F., and on the eighth day the rash appeared. The case was characterized by the intensity of the abdominal symptoms, splenic enlargement, tympany, moderate diarrhœa, and scanty but well-defined eruption. The temperature fell to normal on the twenty-fifth day and to subnormal ranges on the twenty-eighth, when collapse occurred, with an axillary temperature of 94.5° F. After marked oscillations, which continued for several days, the temperature range became that of the man's original condition. This case was treated throughout with calomel injections, and ran a remarkably favorable course.

CASE IV.—D. H., male, æt. 19, laborer, admitted to Ward 2, Bed 30, of the Philadelphia Hospital, on the 23d of January, 1888, on the tenth day of a well-characterized attack of enteric fever, that had been ushered in with a

* The temperature charts, with the exception of those of Cases II., IV., and VIII., are not reproduced for want of space. They were shown at the time of the reading of the paper.



x indicates hypodermic injections of calomel.

CHART I.

CASE II.—Enteric fever. H. O., male, æt. 21.

distinct chill. The temperature on the evening of admission was 104° F.; the following morning, 102.4° F. The patient was delirious, tongue dry and fissured, spleen enlarged, rose spots abundant, stools thin and yellow, from two to five in the course of twenty-four hours, slight epistaxis, moderate tympany.

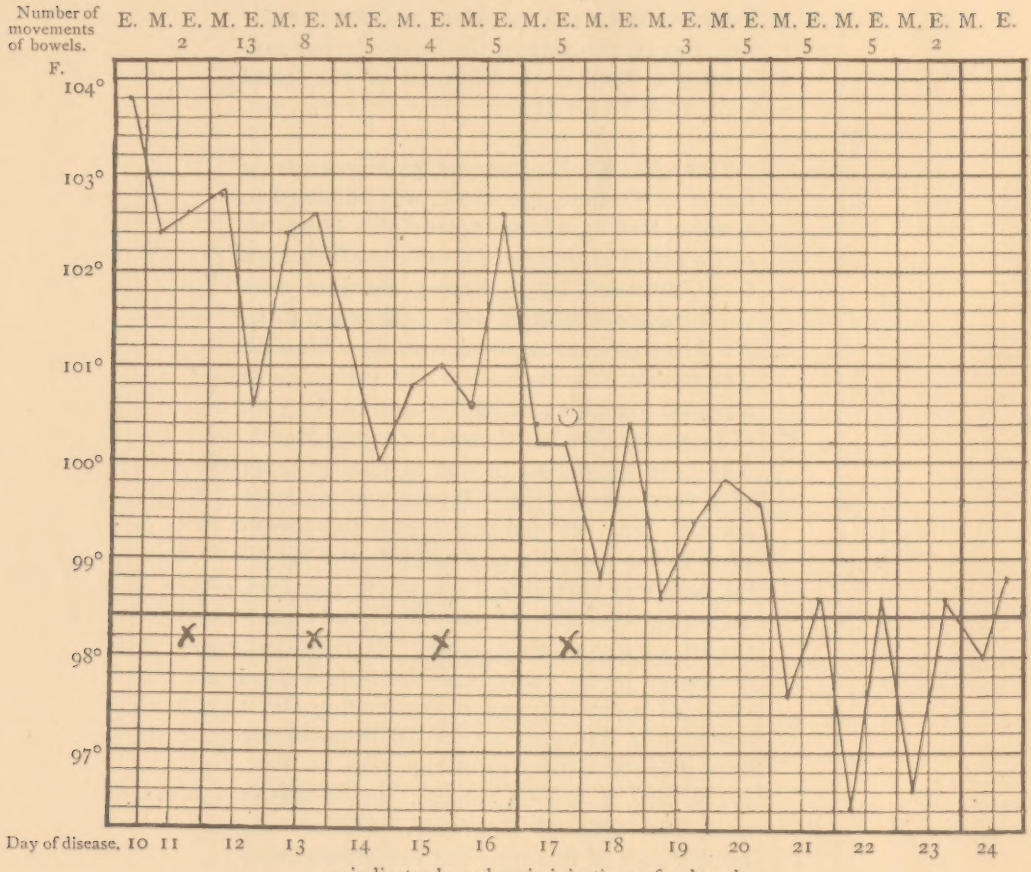
The patient received four intramuscular injections of 1 grain of calomel each in the course of eight days following admission. Defervescence was complete on the twenty-first day of the attack, the form of lysis presenting a distinct modification of the usual type. (See Chart II.)

Case V.—W. N., male, æt. 50, unmarried, a native of Canada, mechanic, was admitted to Ward 2, Bed 13, of the Philadelphia Hospital, on the 6th of January, 1888, suffering from high fever, attended by muttering delirium, with vomiting, constipation, and great prostration. No history could at that time be obtained. The febrile movement, with the exception of a period extending from the 10th to the 18th of February, continued until the 23d of March. The case proved to be one of enteric fever of a very severe type. It was subsequently learned that the sickness began two weeks prior to the patient's admission to the hospital, and was, therefore, of a whole duration, including the afebrile period already mentioned, of about ninety days. It consisted, as shown by an analysis of the temperature chart, of a primary attack, terminating about the 20th of January, succeeded immediately by a relapse, lasting until the 10th of February, and a second relapse, which set in upon the 18th of February. During the greater part of this time the patient was very delirious. A few characteristic rose spots appeared upon the abdomen during each relapse. On the 2d of February intestinal hemorrhage of moderate amount occurred. This patient, from the time of the recognition of the nature of his sickness, was treated by calomel hypodermically. He made a complete recovery, and left the hospital at the end of May.

It is scarcely necessary to say that the foregoing cases of enteric fever were managed in accordance with accepted rules as

CHART II.

CASE IV.—Enteric fever. D. H., male, æt. 19.



x indicates hypodermic injections of calomel.

regards diet, bathing, quietude, and the like. Cold compresses were employed, and repeated 5-grain doses of antipyrin were administered in Case V., when the temperature rose above 104° F. The other cases received no medication other than the hypodermic injections of calomel, except an occasional opium suppository, or dose of bismuth subnitrate, for the control of too frequent diarrhœa, and in one or two instances only a single dose of antipyrin.

PHTHISIS IN SYPHILITIC SUBJECTS.

Case VI.—Widow, æt. 38; ill three years with teasing cough, attended by scanty expectoration, occasional night-sweats, slight loss of flesh, appetite fairly good, evening temperature normal. The history renders it more than probable that the patient suffered from syphilis shortly after her marriage, twelve years ago.

Physical examination revealed extensive dulness over the right lung, anteriorly in the mammary line, with abundant crepitant and subcrepitant râles heard in the infraclavicular area, and extending down the anterior border of the lung. Percussion elsewhere yields good resonance, and especially is this noted in the supraclavicular regions on both sides. Examination of the sputa showed no bacilli.

This patient came under observation the 10th of February, 1888. On the 29th of the same month treatment by hypodermic injections of calomel was commenced, and continued until the end of April, eight injections in all being administered. The area of percussion dulness was then noted to be much less extensive, subcrepitant râles were not heard, and a few crepitant râles only could be detected on forced inspiration after efforts at coughing. The patient left for her home much improved in all respects.*

Case VII.—C. G., male, æt. 35, unmarried, an Englishman, by occupation a painter, was admitted to Ward 2, Bed 25, of the Philadel-

* This is Case IX. of the series in the "Note on the Treatment of Syphilis" in the *Medical News*. It was thought to be a case of gummatous infiltration of the lung. The subsequent history is unknown.

phia Hospital, on the 8th of May, 1888. Syphilis, with well-characterized secondary manifestations, eight years ago; cough and moderate loss of flesh for the past six months; five weeks ago slight blood-spitting, severe pain in the left side, diarrhœa, night-sweats, great shortness of breath. He gives an account of having been tapped three times in the left axillary region, with the removal of bloody fluid. Patient emaciated, extremely sallow, not jaundiced, moderate cough, scanty muco-purulent expectoration, containing numerous bacilli.

The physical signs indicated moderate tubercular infiltration of both apices, with a small cavity on the left side opposite the second intercostal space. Extensive coarse friction sound is heard over the base of the right lung, anteriorly and posteriorly, whereas, in the corresponding position on the left side, there is retraction of the chest and restricted respiratory movement without friction sounds. The night-sweats at the time of admission were profuse and distressing, and the general condition of the patient wretched. The morning temperature ranged about 100° F., and the evening temperature from 102° to 103° F.; the patient weak and depressed, unable to leave his bed.

Treatment by hypodermic injections of calomel was commenced on the 11th of May, and steadily continued, at intervals of four or five days, until the 26th of June, when the patient left the hospital of his own accord, having gained in weight and strength to such an extent that he regarded himself as a well man. The following note is taken from the hospital record:

"Great improvement, subjectively and objectively, no cough or expectoration whatever, no night sweats; for the past fortnight the temperature range has been normal. At the right apex, anteriorly and posteriorly, there are crepitant and subcrepitant râles in abundance. At the right base pleural friction sounds are no longer heard, although patient occasionally complains of sharp pains in this region on deep inspiration. The localized tympanitic percussion resonance in the second intercostal space to the left of the sternum, as previously noted, has disappeared. The dulness on the left side continues very

marked below the clavicle, less so over the mammary region, but increases almost to flatness at the base. On the left side there is faint bronchial respiration, without râles anteriorly, and at the apex posteriorly. Tongue clean; patient looks well, has a good appetite, and weighs one hundred and forty pounds. The finger-nails show a series of well-marked transverse ridges."

This patient had no other treatment whatever except a few doses of picrotoxine for the relief of night-sweats.

PHTHISIS.

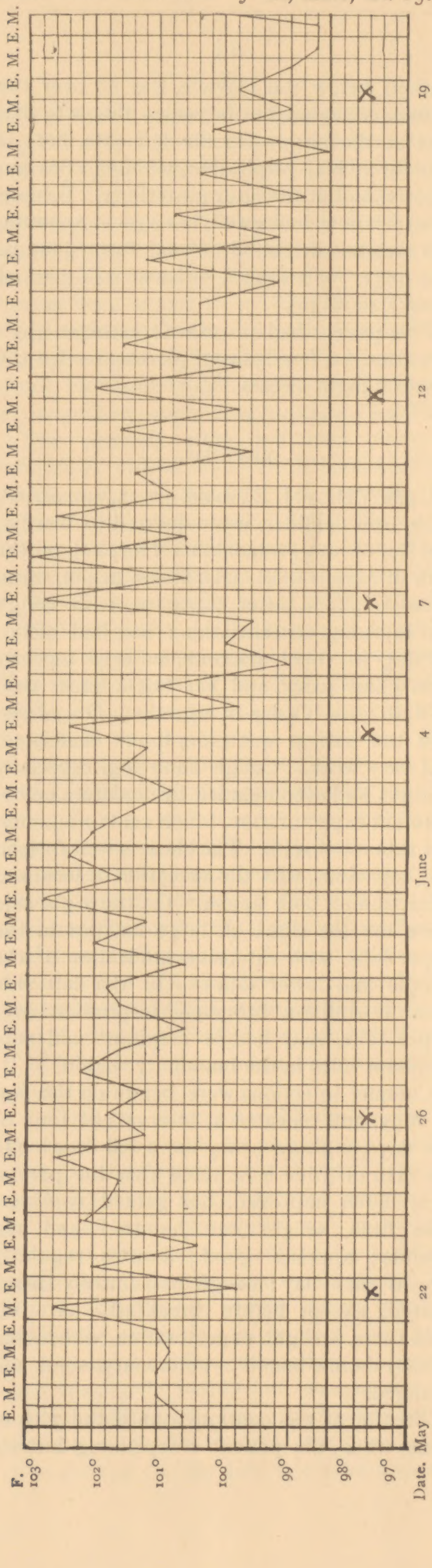
CASE VIII.—J. E., male, æt. 25, unmarried, Irish, iron-moulder, was admitted to Ward 2, Bed 27, of the Philadelphia Hospital, on the 18th of May, 1888. His illness began seven months before, after exposure, with cough and morning expectoration; has had blood-spitting in small amounts, suffered recently from chest pains, and has lost a great deal of flesh: no history of syphilis. On admission the patient was pale, much emaciated, and very weak. Cough annoying, especially at night, and accompanied by moderate muco-purulent expectoration, which contains numerous tubercle-bacilli. The chest is well formed and capacious, with the exception of localized retraction at both apices. On the right side there are the signs of large cavities in the upper lobe, with extensive infiltration of the middle and lower lobes. On the left side there is dulness, bronchial respiration over upper lobe, and coarse crepitant and sub-crepitant râles in the mammary region.

Calomel injections were begun on the 22d of May, and repeated at intervals of four or five days, 2 grains being the usual dose. On the 11th of June it is noted that the patient feels much improved, has gained considerable flesh, weighs one hundred and ten pounds; appetite good; bowels regularly moved each day; cough has entirely disappeared, except before breakfast. At this time there is slight expectoration, which contains tubercle-bacilli; pulmonary signs unchanged.

Treatment was continued until the 30th of June, when, the patient complaining bitterly

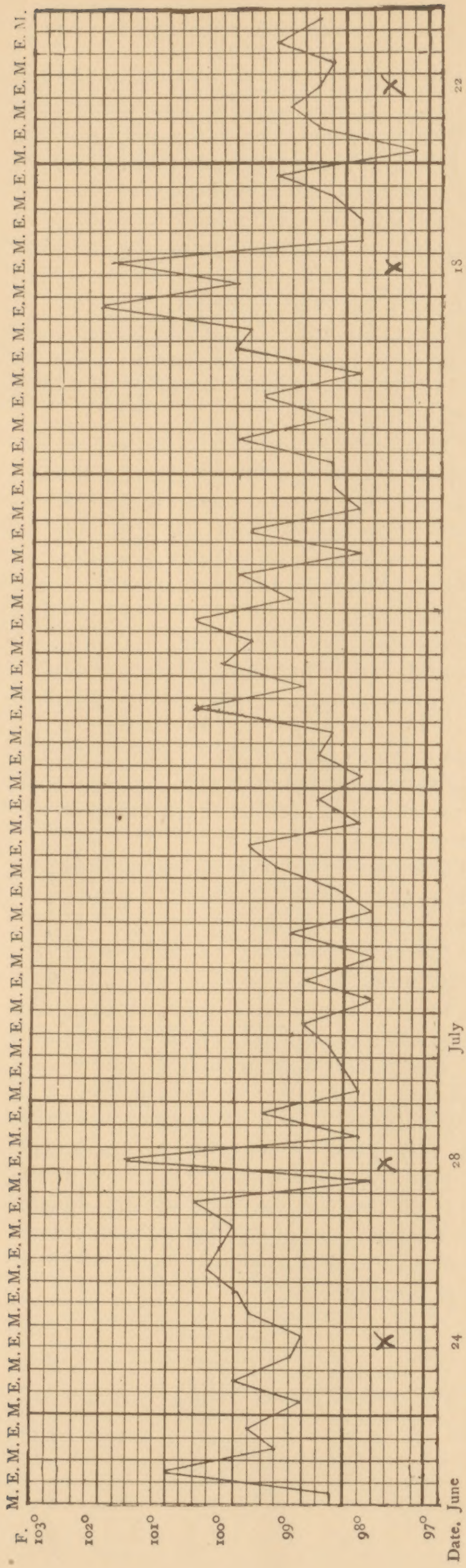
CHART III.

CASE VIII.—Phthisis. J. E., male, æt. 25.



x indicates hypodermic injections of calomel.

CHART III.—*Continued.*



x indicates hypodermic injections of calomel.

of the local pain of the injections, it was stopped. At this time the temperature was practically normal. In the course of eight days the evening temperature rose to 100° F., and in a short time reached 102° F. The calomel injections were then resumed, with the result of speedily bringing the temperature range to the normal. (See Chart III.)

It must be added, though without much bearing upon the case, that this patient during some part of the treatment took at his own request teaspoonful doses of cod-liver oil three times daily.

I have thus systematically treated in accordance with this plan five cases of enteric fever, all of which were severe, and all of which recovered, three of them running an exceptionally favorable course; and three cases of phthisis, in two of which there was a distinct history of syphilis. In the three chest cases marked and rapid amelioration of the constitutional symptoms took place without very great change in the physical signs of local pulmonary trouble. In one of the two cases in which tubercle-bacilli were found, the cough and expectoration wholly disappeared. In the other case, the bacilli persisted in the expectoration.

These cases taken together constitute a clinical experiment, the result of which, considered without prejudice, has forced upon me the conviction that calomel thus introduced into the organism exerts a decided therapeutic influence in ameliorating the symptoms, and in modifying the temperature range of enteric fever and of pulmonary phthisis. In the case of enteric fever with relapses (Case V.) it is impossible to ascribe any very great benefit to the treatment. Nevertheless, those who saw the case in the wards of the hospital were of the opinion that the injections of calomel were on several occasions followed by distinct amelioration of the symptoms.